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Indoor Air Quality

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What Is the Epidemiologic Evidence for a Passive Smoking-Lung Cancer Association?

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Summary

Two survey articles of reports on the association of passive smoking with lung cancer have recently appeared, and also a comprehensive report on the subject of environmental tobacco smoke by a committee of the National Research Council of the United States. The observed excess over a relative risk of unity cannot be explained by chance. Nor can it be fully accounted for by a particular source of bias, the false claims of being non-smokers by individuals who were active or ex-smokers. That possible source of bias leads, in one summary survey, to reducing a relative risk of 1.35 to 1.30, but from 1.34 to 1.15 in the National Research Council report. The latter report suggests that statistical significance would no longer obtain, perhaps, particularly, because of other possible biases. However, to get an estimate of the correct relative risk due to passive smoking, allowance has to be made for actual exposure to passive smoking of those not exposed at home. Thus, the 1.30 is adjusted upwards, by 18 in one survey, to 1.53, but by only 8% in the National Research Council report to 1.24. The National Research Council report had given an anticipated relative risk of 1.1 based on dosimetric considerations. But it is suggested here that that could be as low as 1.05, too low to be detected in an epidemiologic investigation – in any case it would be based on hypothetical assumptions.

In November of 1986 there were two near-simultaneous review articles addressing the subject of passive smoking and lung cancer. One was an invited guest editorial by Blot and Fraumeni in the Journal of the National Cancer Institute, the other a contemporary theme discussion by Wald et al. in the British Medical Journal [1, 2].

There was substantial overlapping in the two articles of the various publications on the subject, and on the basis of which the conclusion of a significant positive association was made. The article by Wald et al. gave, perhaps, more statistical detail about the results of the several studies covered. But, to my mind, there was uncritical acceptance of the results of all the studies. Blot and Fraumeni did suggest that there were some flaws in a particular study, that by Hirayama [3], but decided that any inherent biases in that investigation could not have given rise to the observed elevated risk.

From their overall evaluation of 10 case-control studies (all 10 gave results for females, five separately for males as well) and three prospective studies (two of these covered males separately), which provided 20 separate relative risk (actually odds ratio) values, Wald et al. came up with a summary relative risk of lung cancer due to passive smoking of 1.35 (95% limits 1.19 to 1.54). They trim this down to 1.30 on the basis that some of the presumed non-smokers exposed to passive smoking were actually smokers. Then, on the added basis that even those unexposed to passive smoking at home may still have been exposed when away from home, they raise their estimate of relative risk to 1.53. But note that this last modification presupposes the answer, that passive smoking does

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elevate the risk. For if it did not, there would be no basis for adjusting the 1.30 or 1.35 upwards to 1.53.

Blot and Fraumeni come up with a similar summary measure of relative risk for passive smoking of 1.3 (95% limits of 1.1–1.5), but elevated to 1.7 (95% limits of 1.4–2.1) for heavy passive smoking. These authors suggest that heavy passive smoking is equivalent, at least in terms of nicotine received, to smoking between 1/2 and 3 cigarettes daily, and estimate that smoking a few cigarettes daily would give rise to a relative risk of about 1.5-fold to twofold.

While Blot and Fraumeni do not address the question of correct reporting of non-smoking status, Wald et al. do, having used this as a basis for lowering the relative risk estimate from 1.35 to 1.30. Based on reports and communications from others, Wald et al. estimate that persons reporting themselves as never having smoked (lifelong non-smokers) comprise 2.1% active smokers plus 4.9% former smokers, for a total of 7% ever smokers among the self-claimed never smokers. Wald et al. estimate that these 7% have a combined relative risk of 2, making the assumption in doing this that the active smokers among the 7% smoked on average only a quarter as much as active smokers generally. The relative risk of 2 for the 7% is computed as a weighted average of 3 for active smokers, 1.5 for former smokers, among the 7%.

If 7% of reported never-smokers were actually ex-smokers or active smokers, which were they – the spouses, say, of smokers or the spouses of non-smokers? In my own critique of Hirayama, I had suggested that this false reporting of non-smoking status would preferentially be among those with smoking spouses [4]. If, for example, the 7% overall misreporting of non-smoking status concentrated among spouses of smokers, it would be somewhat higher among persons with smoking spouses who, nevertheless, claimed to be never smokers. Suppose we take it at 20%, in which case the reported lifelong non-smokers relative risk would be 1.20. It could be substantially higher but for the assumption by Wald et al. that the active smokers among the reported never smokers had sharply reduced levels of smoking. However, Wald et al. were ready to make only a small reduction in relative risk for this factor, from 1.35 to 1.30. Their speculative increase, which might have no basis at all, was much greater, from 1.30 to 1.53.

The effect of false reporting of smoking status, specifically of non-smoking, could be much sharper than what Wald et al. have suggested. In a study of biochemical markers of smoke absorption, Jarvis et al. branded as "deceivers" 21 individuals who claimed to be non-smokers [5]. These 21 displayed biochemical patterns very similar to those of actual smokers, not at all like those of accepted non-smokers. The 100 accepted non-smokers comprised 46 without passive smoking, 54 with. Those 21 would constitute 21/121 or about 17% of the total, and these would be active smokers, not just former smokers, or eightfold greater than the 2.1% Wald et al. postulated. Perhaps in the epidemiologic investigations made, false reporting of non-smoking status is at a much lower level, but it would not take much false reporting to account fully for the seeming association between passive smoking and lung cancer.

Recently, a colleague expressed to me the thought that if passive smoking played no role in lung cancer, why are we not finding many negative associations, nor any significantly negative associations? Actually, six of the 20 relative risks reported in Wald et al. are at 1.00 or smaller. And some of those reported as in excess of 1.00 conceal rates of under 1.00. Thus, relative to the rate shown of 1.23 for the study reported by Garfinkel et al., I have brought out in my own critique that that represented a composite of data for various classes of respondents [6, 7]. Where the woman with lung cancer was herself the respondent (as to her husband's level of smoking) the relative risk was 0.83. Using the husbands' responses, the relative risk was 0.77. It was only on the basis of responses by

the sons and daughters, at a time long past when they would have left home, that a relative risk of 3.57 emerged, sufficiently high to raise the overall estimate of relative risk to 1.23. As I indicated in my critique, the replies by the children were more accusatory in nature than revealing of any true relationship.

But even so, it would take 40 large studies to get on average a single seemingly significant negative association of lung cancer with passive smoking, assuming statistical testing at the 5%, two-tailed, level. But we have only 20 evaluations, with many so small that they could not possibly yield any apparently significant protective effect, not even in the unrealistic situation that passive smoking was 100% protective. Suppose a study had a null expectation of only 2 or 3 passive smokers with lung cancer – then there would be some observed number, 5 or 6 or 7 or 8 or more which would be significantly in excess of expectation. But there would be no number, however small or even zero, which would be significantly below expectation. Yet just such low expectations characterize several of the studies reported on by Wald et al. In one study, a relative risk of 2.29 is shown based on only 2 actual cases of lung cancer in passive smokers, expectation 1.20. Another relative risk of 2.45 is based on 3 observed, 1.77 expected. For one prospective study, 4 observed cases have given rise to an estimated relative risk of 3.25, and in another 7 observed cases gave rise to a relative risk of 2.25, suggestive of an expectation little in excess of 3. On the other hand, the four reported risks of under 1.00 had expectations variously of 37.67, 34.08, 6.64 and 13.77.

Of concern to Wald et al. was whether the various relative risks were homogeneous. On this point they cite a chi-square test for heterogeneity of 20.0 on 19 degrees of freedom, $p > 0.2$. However, this is not so much evidence of homogeneity of relative risks as it is reflective of the high unreliability of the individual relative risks. For 8 of the 20 relative risks shown, the upper limit on the relative risk exceeds the lower limit by a factor of about 10 or more, that factor attaining a value of 57 in one instance.

Blot and Fraumeni express concern about other long term consequences of passive smoking, particularly in connection with coronary artery disease. They cite a report by Garland et al. [8] who initially reported a relative risk due to passive smoking of death from ischemic heart disease of 14.9, but seem unaware that the estimate of 14.9 has been revised downward to 2.7. In the report of the National Research Council [9], which I will be discussing below, there is awareness of the downward revision, but not of the fact that the suggestive significance of $p < 0.10$ is lost and becomes $p < 0.20$.

That lung cancer may aggregate in families is also of concern to Blot and Fraumeni, who cite Ooi et al. on the subject [10]. Elsewhere, and yet to appear, I have suggested that apparent familial aggregation, in the instance breast cancer, may be a reflection of an awareness bias rather than of true familial aggregation [11]. If information about relatives is not collected more directly, the apparent aggregation based on reports from the Index case may only reflect heightened knowledge by such cases of similar illnesses about relatives. But the report by Ooi et al. is another instance, like that of Garland et al., in which there has been unreliable statistical evaluation. Thus, Ooi et al. initially reported that the lung cancer risk increased eighteen-fold per 10-year age increase. By letter in the October 1986 issue of the Journal of the National Cancer Institute they have revised that factor downwards, giving separate factors for each 10-year age interval. From age 50 to age 60, the factor is now reported at only 2.9.

The Report of the Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council [9]

I have chosen to discuss the epidemiologic aspects of this Report separately, since it is essentially the definitive work on current knowledge on environmental tobacco smoke. A member of the committee was Nicholas Wald, senior author of one of the articles discussed above. The report contains a technical appendix which largely duplicates the appendix in the article by Wald et al. and also repeats, with minor variations, the data of Wald et al. The body of the report itself contains those same data, but recast differently, and it is the same 13 studies, with 20 relative risk values, which underlie the epidemiologic aspects of the Committee Report.

There are a great variety of issues which the Committee Report goes into, whether physiochemistry, toxicology, assessment of exposures, use of questionnaires, exposure-dose relationships, etc. But my concern at this time is the epidemiology. There could be a point to estimating the annual number of lung cancer deaths in the United States due to passive smoking, but that would have to be on the presumption that passive smoking does play a causative role.

However, the Committee Report is quite restrained in its findings and leaves open the question of whether anything has been established. If the apparent relative risk is significantly greater than unity, the excess cannot be fully explained away by certain biases considered. However, whether there is statistical significance in view of those biases is not addressed.

From dosimetric considerations, the Report suggests that the excess risk of lung cancer due to environmental tobacco smoke should be 1% of the excess risk due to active smoking. This leads to a relative risk of 1.14 for men, perhaps less for women. From the epidemiologic data, the summary relative risk is 1.34, but it is brought out that for United States studies only the relative risk would be only 1.14. If only large studies are considered, the overall relative risk would be 1.32.

Next addressed by the Report is the effect of biases, particularly the bias associated with the false reporting of individuals that they were not (or never have been) smokers. This leads to a lowering of the estimated relative risk of 1.34 (or 1.30 to 1.34) to 1.15. But note that on this same basis, Wald et al. were willing to reduce an apparent relative risk of 1.35 only slightly, to 1.30.

Yet another adjustment is made. If non-smokers are not exposed to environmental tobacco smoke at home, they might still be exposed to it away from home. An upward adjustment of 8% on account of this yields $1.15 \times 1.08 = 1.24$. This contrasts with the upward adjustment of 18% made by Wald et al., who calculated $1.30 \times 1.18 = 1.53$. The Committee Report differs markedly from the separate report made by one of its own members.

In discussing Wald et al. I suggested that the upward modification they have presupposed a positive role for passive smoking. This same thing is true for the 8% upward adjustment in the Committee Report. For purposes of evaluating the statistical significance of the findings, the relative risk should be taken as 1.15, though the value of 1.24 might be appropriate for assessing the toll in excess lung cancer due to passive smoking assuming that there is causality. With the United States studies indicating an unadjusted relative risk of only 1.14 rather than 1.34, both the 1.15 and the 1.24 might be sharply lowered if intended to apply only to the United States.

But let me stay with the relative risk of 1.15 prior to the 8% upward adjustment. Is that relative risk significantly in excess of 1.00? I suspect not. And even the question of bias remains open. Both in the Committee Report and in the article by Wald et al., the only

biases factored in were just those that would fit into neat mathematical formulas. More subtle biases or ones that had not been thought of did not get in. I gave an example above of the use by Garfinkel et al. of the responses by sons and daughters of the level of smoking by the fathers.

I might even speculate about publishing bias. If an investigator got a weakly or insignificantly negative result for the role of passive smoking in lung cancer, would he bother submitting it for publication? And if he did, would it be accepted for publication? Postulating this kind of bias is not necessary for establishing that the 1.15 relative risk is likely not significant. But I bring it up in connection with a tendency I see towards accepting uncritically or less critically manuscripts which are on the right side of the fence on the issue of passive smoking. A particular example was the publication of the article by Garland et al. on passive smoking and ischemic heart disease mortality, the claims of which fell apart on scrutiny.

Let me bring up now another thought. Some time ago the possibility of subtle or not-so-subtle biases in case-control or other epidemiologic investigations was so much a matter of concern that it was suggested that unless the relative risk were at least 2.0, any increase in risk should not be accepted. Perhaps we can do better now and might employ a less restrictive criterion.

But I can see no relaxation to the point of accepting the relative risks now observed for passive smoking in lung cancer. What we must accept is that it is unlikely that any epidemiologic investigation has been on can be mounted which would establish a causal role for passive smoking in lung cancer. Those who believe such a role exists should continue to believe as much, and might even hazard estimates as to the resulting toll in deaths and disease, with other allowed to hold contrary beliefs. What would be incorrect would be to claim that epidemiologic studies have established the correctness of the belief.

If epidemiologic investigations cannot establish a role for passive smoking, the best we can do is to make suppositions estimates of how great that role may be – and such suppositions estimates can be too high if any of the underlying supposals are false. One supposal would be that the dosage response curve is linear through the origin, another that some particular biochemical measure, say level of cotinine, is a proper measure of the equivalent exposure to cigarettes of passive smoking. And, I point out, there could be the assumption that the temperature at which tobacco smoke is inhaled is not relevant, though I would think that fresh hot smoke would be more active than stale smoke.

With this thought in mind, we can pick up some clues from the report of Jarvis et al. who, after excluding "deceivers", report average cotinine levels in plasma, saliva, and urine of 100 non-smokers to be at 0.55%, 0.55% and 0.364 respectively of those levels from 94 smokers. Let us take it at 0.5%. If the average cigarette smoker has a relative risk for lung cancer of 10.0 (enhancement of 900%, though the enhancement may be 1,400% for very active smokers), this would put the enhanced risk due to environmental tobacco smoke at 4.5%, for a relative risk of 1.045 (it would be 1.07 using the 1,400% enhancement for very active smokers). That relative risk, 1.045, would encompass both passive smoking at home and away from home, including individuals not exposed to passive smoking at home.

What matters, however, relative to the conduct of epidemiologic studies on the subject, is the differential in relative risk between those knowingly exposed to passive smoking and those who believe themselves unexposed. From data available in Jarvis et al., it would appear that those seemingly not exposed to passive smoke (46 in number) nevertheless have a relative risk of about 1.02. For the 54 non-smokers claimed to be actually exposed to passive smoking, the relative risk based on cotinine levels would, in

similar manner, be 1.07. Compared then to seemingly non-exposed to passive smoking, the calculated relative risk for the known exposed to passive smoking would be 1.05. That small increase in relative risk just would not show up on any epidemiologic investigation and would be submerged, in any case, by other very likely biases. The National Research Council report had suggested a relative risk, based on dosimetric considerations, of 1.14, but on the assumption that enhancement in risk due to an active smoking was 1,400%. An enhancement of 900% would have led them to anticipated relative risk of 1.09. But whether we use 1.05, 1.09, or 1.14, the effect would still be undetectable.

As a last point, I raise the issue of passive smoking effects on children. If parents can be shamed into not exposing their children to passive smoking, this is all well and good, even if the supporting basis is unsound. I note that the ill effects arise mostly in early childhood, and have two questions. Have the passive smoking effects been isolated from effects due to mother's smoking prior to the child's birth? To what extent has account been taken that cigarette smoking concentrates in families with lower socio-economic status, as evidenced by lower educational level and more unemployment etc. Rona et al. also brought in the factor of overcrowding at home in their report that passive smoking resulted in some small reduction in the stature of children [12]. But even Rona et al. failed to take properly into account, as I have suggested, the role of some of these important factors on smoking rates in their evaluation [13].

What with subtle biases, not so subtle biases, and even extravagant errors, one should not accept too readily claimed demonstrations of ill effects of passive smoking. Passive smoking has been the favorite whipping boy of epidemiologists for too long already. The public is entitled not to be unnecessarily exposed to environmental tobacco smoke but any panic is unjustified.

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